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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,649	09/29/2005	Yechezkel Barenholz	BARENHOLZ9A	5688

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EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,649	BARENHOLZ ET AL.	
	Examiner	Art Unit	
	ISAAC SHOMER	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8,10,11,13,14,16-20 and 26* is/are pending in the application.

4a) Of the above claim(s) *17-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,10,11,13,14,16 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *27 December 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 27 September 2010 has been entered, and the arguments presented therein have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-8, 10, 11, 13, 14, 16, and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The limitation “the components being selected such that he lipid assembly is chemically and physically stable under storage conditions of 4 [degrees Celsius] in

biological fluids for at least six months" is indefinite. This is because it is unclear what is meant by "stable" for the reasons set forth below:

The specification provides details of four different tests conducted to determine stability, as of the section entitled "Stability of lipid assemblies comprising biologically active lipids" on pages 42 and 43 of the specification. The description of these tests is insufficient for the following reasons:

Chemical Stability test (a): Applicant discloses that "Measurement of dispersion" is conducted with a pH meter. However, applicant does not specify which pH ranges are considered stable, and which pH ranges are considered unstable.

Chemical Stability test (b): Applicant discloses that phospholipid acylester hydrolysis is measured by specific procedures, and references are given for said procedure. However, applicant does not disclose what levels of hydrolysis are considered sufficiently stable, and would levels of hydrolysis would result in a lipid assembly that is unstable.

Physical Stability test (a): Applicant discloses that assembly size distribution is conducted by dynamic light scattering, as of page 42 of the spec, part (a) under physical stability. However, applicant does not disclose which sizes are considered stable, and which sizes are considered unstable.

Physical Stability test (b): Applicant discloses that level of free, non-aggregated biologically active lipid is determined by TLC (thin layer chromatography). However, applicant does not disclose what levels of free lipid are required for the lipid assembly to be considered unstable.

Furthermore, not only are the different types of stability outlined above unclear, but the claim is also indefinite because it is unclear which of these measure(s) (or combination thereof) is required to be met by the claimed lipid assembly.

Claim Rejections - 35 USC § 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 10, 11, 13, 14, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Needham (US Patent 6,200,598) as evidenced by Israelachvili et al. (Quarterly Reviews of Biophysics, Vol. 13, 2, 1980, pages 121-200, wherein pages 122-164 are included), Kumar (Proc. Natl. Acad. Sci., Vol. 88, January 1991, pages 444-448), and Tirosh et al. (Biophysical Journal, Vol. 74, March 1998, pages 1371-1379).

Needham is drawn to temperature sensitive liposomes, as of Needham, abstract. In one embodiment, Needham teaches a liposome comprising:

- dipalmitoylphosphatidylcholine (DPPC) (reading on part c of claim 1)
- monophosphatidylcholine (MPPC) (reading on part a of claim 1)
- and distearoylphosphatidylcholine modified with polyethylene glycol (DSPE-PEG) (reading on part b of claim 1), wherein said PEG has a molecular weight of 2000, as of Needhman, Example 5, column 16 lines 10-17.

These are present in a ratio of DPPC:MPPC:DSPE-PEG of 85.935:9.545:4.520, as of Needham, Example 5, column 16 lines 10-17.

While Needham does not use the term non-liposome forming lipid, the skilled artisan would have understood that MPPC is a non-liposome forming lipid. This is because MPPC stands for monophosphatidylcholine and is a lysolipid (i.e. a lysophospholipid), as of Needham, column 2 line 33. Lysophospholipids are taught to form either spherical micelles, globular micelles, or cylindrical micelles, as of Israelachvili et al. (hereafter referred to as Israelachvili), page 158, Figure 4.2, specifically the first two lines of the figure which teach "some lysophospholpids" on the first line and "lysolecithin" on the second line. As liposomes are made of bilayers and not micellar structures, the skilled artisan would have understood that MPPC is a micelle forming lipid and not a liposome forming lipid.

While Needham does not specifically teach that MPPC is a “biologically active lipid,” (as required by part (a) of claim 1), the skilled artisan would have understood that MPPC would have met this limitation. Support for this position is provided by Needham, abstract, wherein Needham teaches that lysolipid increases the amount of active agent released by the liposome at a phase transition temperature. As such, MPPC, which is a lysolipid, would have had an effect on the biological activity of the liposome and therefore would have been biologically active.

While Needham does not teach the atomic mass ratio of the headgroup to the hydrophobic region in the lipid MPPC, the skilled artisan would have understood that said ratio would have been at least 0.3 as required by claim 1. Said lipid would have

comprised a hydrophilic phosphate and choline headgroup, with a molecular formula of $N(CH_3)_3$-CH_2-CH_2-O-PO_2-O-, wherein said group has a molecular weight of 184 Daltons. Said lipid would have comprised a single palmitoyl chain with a molecular formula of $(C_{15}H_{31})$-CO, wherein said chain would have had a molecular weight of 239 Daltons. As such, a ratio of 184/239 is about 0.77, which exceeds 0.3, as required by part (a) of claim 1.

Needham does not specifically teach that the composition is stable under storage conditions of 4 degrees Celsius in biological fluids for 6 months, as this exact criterion was not tested. However, it does appear that the liposomes of Needham would have been stable at low temperature. Support for this position is provided by the thermograms as of Needham, Figures 5A, 6A, and 6B, which show a phase transition at around 40 degrees Celsius, but no phase transition at lower temperatures. Furthermore, the presence of MPPC appears to result in a peak on a thermogram at a lower temperature (about 35 C), as shown by Needham, Figure 5A. As such, the skilled artisan would have expected that the liposomes of Needham would have been stable at the temperature of 4 C (which is lower than those tested by Needham), and that the presence of MPPC would have enhanced thermal stability as compared with a liposome lacking MPPC.

As to claim 2, Needham is silent as to the additive packing parameter of the lipid assembly. However, the composition of Needham is a liposome, as of Needham, abstract. The skilled artisan would have understood that a liposome comprises a bilayer. Kumar provides evidence that a lipid assembly that comprises a bilayer has an

additive packing parameter of 0.74 or greater, as of Kumar, page 447, left column, first paragraph of discussion section. As such, the skilled artisan would have understood that the additive packing parameter of the liposome of Needham would have been 0.74 or greater.

As to claim 3, Needham is silent as to the number of water molecules bound to the lipopolymer headgroup, which, in the example of Needham, is PEG with a molecular weight of 2000, as of Needhman, Example 5, column 16 lines 10-17. The skilled artisan would have expected that in the hydrated state, a PEG moiety with a molecular weight of 2000 would have comprised at least 60 water molecules per headgroup. Evidence for this is provided by Tirosh et al. (hereafter referred to as Tirosh). Tirosh teaches that the hydration number of PEG is about 136, which is understood to read on the fact that there are at least 136 water molecules per PEG moiety, as of Tirosh, page 1373, right column Table 1. As such, the skilled artisan would have understood that the PEG groups in the liposome of Needham tightly bind at least 60 water molecules, as required by claim 3.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 5 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Needham (US Patent 6,200,598) as applied to claims 1-3, 10, 11, 13, 14, and 16 above under 35 U.S.C. 102 above.

Needham teaches a liposome comprising DPPC, MPPC, and DSPE-PEG. See the above rejection. Needman suggests the inclusion of ceramide, as of Needham, column 5 line 60 (as required by claim 5). Needham teaches that the liposome may be hydrated with an aqueous preparation, as of Needham, column 2 line 22, wherein water is understood to be a physiologically acceptable carrier as required by claim 26. Needham suggests that the composition be used to administer an active agent to a target site and thereby impart a therapeutic effect, as of Needham, column 18 claim 16.

The instant prior art does not appear to provide sufficient specificity, i.e., involves too much "picking and choosing" to give rise to anticipation. *See*, Corning Glass Works v. Sumitomo Elec., 868 F.2d 1251, 1262 (Fed. Circ. 1989). That being said, it must be remembered that "[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect…. the combination is obvious". KSR v. Teleflex, 127 S,Ct. 1727, 1740 (2007)(quoting Sakraida v. A.G. Pro, 425 U.S. 273, 282 (1976)). Consistent with this reasoning, it would have obvious to have selected the various combinations of features claimed from within the prior art disclosure, specifically a ceramide (as required by claim 5), water as a physiologically acceptable carrier, and use at a target site (as required by claim 26), to arrive at the instantly claimed compositions.

Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Needham (US Patent 6,200,598) as applied to claims 1-3, 10, 11, 13, 14, and 16 above under 35 U.S.C. 102 above, and further in view of Wei et al. (US Patent 5,677,337).

Needham teaches a liposome comprising DPPC, MPPC, and DSPE-PEG. See the above rejection. In a separate embodiment, Needham teaches the incorporation of "therapeutic lipids," as of Needham, column 5 lines 60-62. Needham also teaches the inclusion of therapeutic agents such as doxorubicin, paclitaxel, and methotrexate (among others), as of Needham, column 17 lines 17-21, all of which are known by one of ordinary skill in the art to be anti-cancer agents.

Needham does not teach a ceramide wherein said ceramide is a C2-C26 ceramide.

Wei et al. (hereafter referred to as Wei) teaches a liposome comprising phosphatidylcholine, cholesterol, and either C2-ceramide or C6 ceramide, as of Wei, column 15 lines 11-25. Wei teaches that the liposomes of the invention are used to treat cancer, as of Wei, column 4 lines 38-42. This occurs because ceramides stimulate apoptosis, as of Wei, column 2 lines 20-22, and prevent cell proliferation, as of Wei, column 2 lines 38-42.

It would have been prima facie obvious for one of ordinary skill in the art to have included C2 ceramide or C6 ceramide, as of Wei, in the liposome of Needham. This is because the above ceramides would have predictably had a therapeutic effect against cancer, as it they are taught to promote apoptosis by Wei. As Needham suggests the inclusion of anti-cancer therapeutics as well as therapeutic lipids, the skilled artisan

would have been motivated to have added a lipid with a therapeutic effect against cancer to the liposome of Needham. As such, the skilled artisan would have been motivated to have added the above ceramides to the liposome of Needham to have predictably had a therapeutic effect against cancer with a reasonable expectation of success.

Claims 6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Needham (US Patent 6,200,598) as applied to claims 1-3, 10, 11, 13, 14, and 16 above under 35 U.S.C. 102 above, and further in view of Igarashi et al. (US Patent 5,137,919).

Needham teaches a liposome comprising DPPC, MPPC, and DSPE-PEG. See the above rejection. In a separate embodiment, Needham teaches the incorporation of "therapeutic lipids," as of Needham, column 5 lines 60-62. Needham also teaches the inclusion of therapeutic agents such as doxorubicin, paclitaxel, and methotrexate (among others), as of Needham, column 17 lines 17-21, all of which are known by one of ordinary skill in the art to be anti-cancer agents.

Needham does not teach N,N-dimethylsphingosine (DMS).

Igarashi et al. (hereafter referred to as Igarashi) is drawn compounds having a profound effect on mammalian cell proliferation, as of Igarashi, column 1 lines 9-11. In one embodiment, Igarashi teaches the effect of N,N-dimethylsphingosine and N,N,N-trimethylsphingosine against cancer cells, as of Igarashi, column 2 lines 40-50 and Figures 2A-2C, which show that both compounds have an effect against a cancer cell line.

It would have been prima facie obvious for one of ordinary skill in the art to have included N,N-dimethylsphingosine, as of Igarashi, in the liposome of Needham. This is because N,N-dimethylsphingosine would have predictably had a therapeutic effect against cancer, as it is taught by Igarashi to kill cancer cells. As Needham suggests the inclusion of anti-cancer therapeutics as well as therapeutic lipids, the skilled artisan would have been motivated to have added a lipid with a therapeutic effect against cancer to the liposome of Needham. As such, the skilled artisan would have been motivated to have added the lipid N,N-dimethylsphingosine to the liposome of Needham to have predictably had a therapeutic effect against cancer with a reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612